STOCHASTIC DIFFERENTIAL EQUATIONS MODELLING OF LEVODOPA CONCENTRATION IN PATIENTS WITH PARKINSON'S DISEASE

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BACKGROUND

- Westin et al. [1] developed a pharmacokinetic-pharmacodynamics model for duodenal levodopa infusion described by four Ordinary Differential Equations (ODE), the first three of which define the pharmacokinetic model.

OBJECTIVES

- **Introduce stochasticity** in the pharmacokinetic model of levodopa concentration to check **whether inter-individual variability may be separated into measurement noise and system noise**.
- Investigate **whether the SDE based model provide better fits** than the ODE counterpart, by using a real data set.

METHOD – DATA USED

- Pooled from 2 studies investigated by Westin et al. [1]
- First study had 3 patients, who were given bolus dose in the morning. Data was collected for 2 hours on two non-consecutive days.
- Second study had 5 patients with 3 occasions each. Data was collected on the patients for 4 hour-periods with five different infusion rates in 2.5 days.
- Plasma samples were anlyzed by high performance chromatography.

METHOD – MODELLING

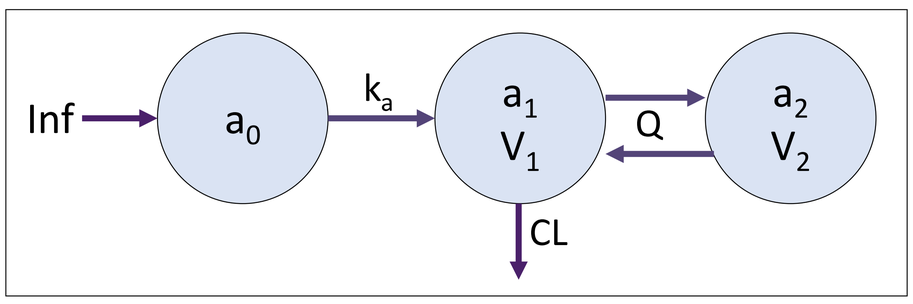


Fig 1. Structural PK model adopted from Westin et al [1]. Inf - Levodopa infusion (mg/min); a_i – amount (mg) in compartment i; V_i – apparent volume (L) in compartment i; Q – inter-compartmental clearance (L/min); CL – clearance (L/min).

- **System noise variables** are added to the previously developed ODE model through a standard Wiener process (Brownian motion) [2], as shown below.

$$\frac{da_0}{dt} = Inf - k_a a_o + \sigma_w dw \quad (1)$$

$$\frac{da_1}{dt} = BIO.k_a a_0 - \left(\frac{Q}{V_1} + \frac{CL}{V_1}\right) a_1 + \left(\frac{Q}{V_2}\right) a_2 + \sigma_w dw \quad (2)$$

$$\frac{da_2}{dt} = \left(\frac{Q}{V_1}\right) a_1 - \left(\frac{Q}{V_2}\right) a_2 + \sigma_w dw \quad (3)$$

BIO – bioavailability (fraction absorbed); $\sigma_w dw$ – system noise.

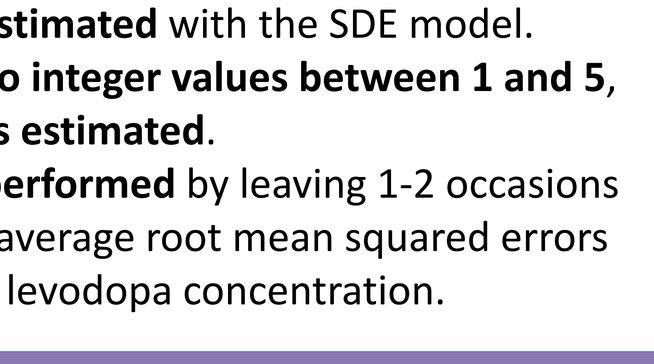
METHOD – DATA ANALYSIS

- The R package **PSM** [3] is used for modelling levodopa concentration and parameter estimation.
- First, the diffusion scale parameter, $\boldsymbol{\sigma_w}$, **and bioavailability are estimated** with the SDE model.
- Second, $\boldsymbol{\sigma_w}$ is **fixed to integer values between 1 and 5**, and **bioavailability is estimated**.
- **Cross-validation is performed** by leaving 1-2 occasions out to compare the average root mean squared errors (RMSE) of predicted levodopa concentration.

RESULTS

- Both models estimated bioavailability to be about **88%**.
- The **SDE model converged** for all values of σ_w ranging from 0 to 5.
- The average **RMSE for the ODE model** was found to be **0.298**, and the lowest average **RMSE for the SDE model** was **0.275** when $\boldsymbol{\sigma_w}$ was fixed to **4**.

Fig 2 (right). Cross-validation results - average RMSE of levodopa concentration at fixed values of σ_w.



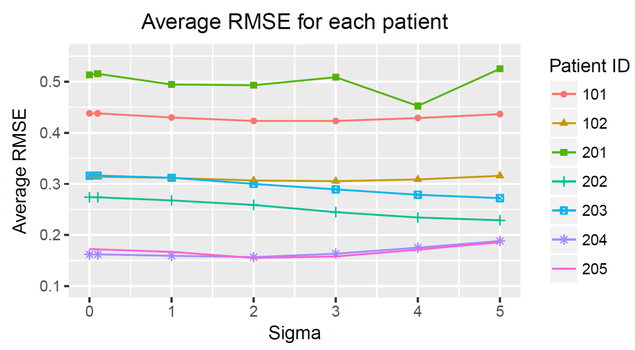


Fig 3 (left). Cross-validation results - average RMSE of levodopa concentration for each patient at fixed values of σ_w.

CONCLUSION

- Both models estimated similar values for bioavailability. The non-zero σ_w estimate implies that **the inter-individual variability may be separated**.
- However, the improvement in the predictive performance of the SDE model turned out to be rather small, compared to the ODE model.

REFERENCES

[1] J. Westin, D. Nyholm, S. Plhagen, T. Willows, T. Groth, M. Dougherty, and M. O. Karlsson. A pharmacokinetic-pharmacodynamic model for duodenal levodopa infusion. *Clinical Neuropharmacology*, **34**, 2011, 61-5.
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